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Letter to the Editor

Premature Adrenal Cortical Dysfunction in Mandibuloacral Dysplasia: A Progeroid-Like Syndrome†

To the Editor:

Mandibuloacral dysplasia (MAD; OMIM #248370) is a rare progeria-like autosomal recessive syndrome characterized by postnatal onset of progressive osteolysis of the clavicles and distal phalanges, progressive mandibular hypoplasia (resulting in dental crowding), flexion contractures, thin/beaked nose, prominent eyes, alopecia/thin hair, mottled cutaneous hyperpigmentation with premature skin atrophy of the limbs and nail dysplasia, partial lipodystrophy, and wormian bones of the skull. Associated endocrine dysfunction consists of hypogonadism, insulin-resistant diabetes mellitus, and hyperlipidemia [Cutler et al., 1991].

Progeroid syndromes offer a unique opportunity to study aging of the endocrine system. Prompted by symptoms of adrenal androgen deficiency in a patient with MAD and hypogonadism and who was already receiving replacement doses of testosterone, we studied his adrenocortical function. The patient had decreased basal levels of Δ5-steroids and a blunted response to adrenocorticotropin (ACTH) stimulation, findings similar to those of elderly individuals and of other patients with adrenal *zona reticularis* dysfunction.

The patient was a 52-year-old Caucasian man with MAD, who was first reported elsewhere, as a variant of Werner syndrome [Cohen et al., 1973]. He developed normally until he was age 4 years, when it was noticed that he had thin legs. Between ages 6 and 12 years, he experienced numerous problems with dental crowding and caries requiring extensive dental treatment. At age 14 years, he was still prepubertal. His testicles were not palpable on examination. Bilateral inguinal canal exploration found atrophic testes in the scrotum. They were excised, and the microscopic examination showed the seminiferous tubules to be composed of "solid nodules of cells without evidence of differentiation." The histological diagnosis was consistent with testicular hypoplasia and the patient was started on replacement doses of testosterone. Growth hormone deficiency was also documented by stimulatory testing, and the patient received growth hormone therapy until he reached a final height of 178 cm. At age 18 years he was diagnosed with bilateral sensorineural hearing loss and, by that time, he had significant other changes consistent with premature aging. At age 24 years, he was diagnosed with diabetes mellitus; biochemical studies showed hyperinsulinemia, hypercholesterolemia, and hyper-prebetalipoproteinemia. However, diet and a short medical treatment brought his diabetes under control. The patient was evaluated recently in our institution for fatigue, dryness of the skin, and an overall "decreased sense of well-being" despite years of treatment with appropriate endocrine replacement.

On examination, the patient was anxious. All of his findings have been described previously [Cohen et al., 1973], but they appeared accentuated in relationship to his previously published picture (the patient declined photography during this evaluation): he had "pseudo"-proptosis, secondary to lack of subcutaneous periorbital fat, a thin/beak-like nose, hypoplasia of the mandible with retrognathia, and bilateral arcus senilis; he had taut, atrophic, hyperpigmented, scarred skin on his limbs and face. The chest was broad, with widespaced nipples. There was no evidence of gynecomastia. His body exhibited general lipodystrophy. The abdomen was protuberant without hepatosplenomegaly. He had Tanner IV pubic hair distribution and a micropenis with a stretched penile length of 7 cm. He had bilateral testicular implants. There was limited range of motion in the fingers and toes. He was unable to close either fist. His feet were narrow. The palmar and plantar surfaces of the hands and feet were remarkable for the absence of subcutaneous fat. He had normal intelligence and normal neurological findings.

His mid-treatment testosterone level was 422 ng/dL (on 200 mg of testosterone enanthate intramuscularly biweekly). Results of thyroid function tests were normal. His fasting glucose level was 84 mg/dL, cholesterol 212 mg/dL, and LDL cholesterol 169 mg/dL. An ACTH stimulation test using the synthetic 1–24 analog Synachten (given at 250 mcg/dose, intravenously) was administered, and blood samples were drawn at 0, 30, and 60 min after injection. Basal level of cortisol and the absolute rise of cortisol following ACTH stimula-

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TABLE I. ACTH Stimulation Test of Patient at Age 48 Years

adrenocorticotropin (ACTH) stimulation time point	17-OH Pregnenolone ng/dL	17-OH Progesterone ng/dL	Δ4/Δ5 steroids ratio (prog/preg)	Cortisol μg/dL	DHEA ng/dL	Androstenedione ng/dL
0 min	15 (27.9 ± 8.1)[a]	13 (218.8 ± 37.4)[a]	0.866 (7.84)	14.6 (13.5 ± 4.2)[a]	47 (47.6 ± 6.1)[a]	46 (215 ± 35)[a]
30 min	847 (41 ± 8.33)[a]	312 (70.5 ± 16.6)[a]	0.368 (1.72)	24.0 (26.2 ± 5.4)[a]	216 (346 ± 128)[a]	108 (67 ± 17)[a]
60 min	726 (65.3 ± 10.3)[a]	272 (94.3 ± 21.5)[a]	0.375 (1.44)	27.4 (30.9 ± 6.4)[a]	248 (471 ± 198)[a]	121 (94 ± 22)[a]

[a]Reference values (mean ± SD) [Rohmer et al., 1990; Nestler et al., 1992].

tion were normal (Table I). Basal levels of all adrenal androgens were low as compared with normative values [Pakarinen et al*.,* 1979; Rohmer et al., 1990; Nestler et al., 1992]. At baseline, there was an inversion of the Δ4/Δ5 ratio that persisted after ACTH stimulation suggesting 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency. In addition, the blunted rise of dehydroepindrosterone (DHEA) to ACTH stimulation, compared with that of normal controls, suggested a markedly diminished 17,20-lyase enzymatic activity (Table I).

Compromised adrenal androgen secretion in a patient with a progeroid-like syndrome is consistent with the decreased basal levels of DHEA and diminished Δ5-steroid response to acute ACTH stimulation in the elderly [Arlt et al., 1999; Bélanger et al., 1994]. A reduction of 3β-HSD activity has not been reported with normal aging; in contrast, a reduction of 3β-HSD activity in the *zona reticularis* may be responsible for the rise in DHEA and its sulfated product (DHEA-S) production during pubarche [Lee et al., 1975; Gell et al., 1998]. However, because 3β-HSD is a competitor of 17,20-lyase through the removal of steroid precursors [Pakarinen et al., 1979], it is possible that decreased 3β-HSD activity in our patient represents a compensatory response to maintain DHEA/DHEA-S levels in the presence of a premature reduction of 17,20 lyase activity.

The decline of basal levels of adrenal androgens along with blunted response to acute ACTH stimulation is a well-known effect of aging [Vermeulin et al., 1981]. Parker et al. [1999] have observed that the *zona reticularis* is reduced in size compared with the rest of the adrenal cortex in aging men. DHEA sulfotransferase activity is diminished in the adrenals of aging men and women compared with young adults [Orentreich et al., 1984]. They proposed that "most if not all of the age-associated deficiency in adrenal androgen production is due to changes in the maintenance of the functional and morphological integrity of the *zona reticularis*." Some of these changes, however, may also be related to hyperinsulinemia, at least in some patients, including the subject of this report [Nestler et al., 1992].

Genetic syndromes associated with premature aging offer a model for the study of "adrenopause." The investigation into the exact roles of DHEA and DHEA-S in age-related changes are ongoing. Administration of DHEA to women with adrenal insufficiency resulted in significant improvement of their sense of well being and sexuality [Morales et al*.,* 1994; Arlt et al., 1999]. Epidemiological data support beneficial effects of DHEA and DHEA-S: low DHEA-S is correlated with an increase in cardiovascular morbidity in men, an increase of breast cancer in women, and a decline in immunocompetency during aging [Labrie et al., 1997]. Morales et al. [1998] reported on a 6-month treatment with 100 mg per day of DHEA in men and women of advanced age. Results revealed a decrease in percentage body fat, an increase in knee muscle strength and lumbar back strength in the men, but not in the women. Total body mass increased in women, but not in men, whereas an increase in serum somatomedin C was measurable in both genders.

We conclude that our patient with MAD, as perhaps other patients with progeroid-like syndromes, had dysfunction of the *zona reticularis* consistent with what one sees in the elderly, which is a marked decrease in 17,20-lyase activity, along with a significant but possibly compensatory decrease of 3β-HSD activity. It remains to be seen whether accelerated adrenal androgen failure in our patient was related to primary senescence of the adrenal cortex or resulted from a secondary response to the generalized aging process ongoing in his condition.

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